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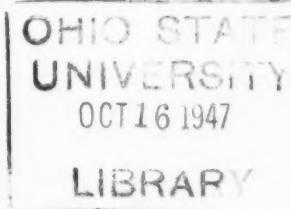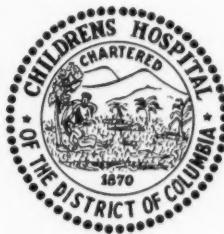
ROCKY MOUNTAIN SPOTTED FEVER TREATED WITH PARA-AMINO BENZOIC ACID*

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The present report deals with the general considerations of 36 cases of Rocky Mountain Spotted Fever observed at The Children's Hospital, Washington, D. C. between 1931 and 1946, and the specific management of 8 cases treated in the summer of 1946 with para-amino benzoic acid.

INTRODUCTION

The identification of the disease in the East by Badger, Dyer and Rumreich[1] in 1931 was followed by the rapid recognition of its prevalence in the central and eastern states. Since 1940 reports of Rocky Mountain spotted fever have come from almost all over the United States, the total annual incidence of reported cases ranging from 400 to 500. In the East the highest incidence is in Maryland, Virginia and North Carolina. In the Rocky Mountain and Pacific coast states the wood tick, Dermacentor Andersoni, is responsible for transmission to man. In the East and South the dog tick, Dermacentor variablis is the important carrier.

The total number of cases in the United States reported for the 5 years, 1933-1937 inclusive, was 2990 with 420 deaths[2]; of these, 1435 cases and 273 deaths were from the Mountain and Pacific states with a death rate of 19.4%. In 1944, there were 470 cases with 130 deaths. The mortality varies greatly but remains fairly constant in different localities. In the Bitter Root Valley it was over 80% for adults and 27.5% for children. The case fatality rate for the entire United States is about 22% and is influenced by the age of the individual rather than by geographic location. In all regions the disease is much more fatal in adults than in children.

In the 16 year series at Children's Hospital there was a mortality rate of 8.3% with 3 deaths in 36 cases. The age incidence of the 36 patients ranged from 15 months to 13 years, the average being 5 years. Of these 61.2% were males and 38.8% females. The high incidence among males is explained by the playing habits of boys, presenting a greater liability to exposure. In this series 91.7% were white and 8.3% were colored. Nine or 25% (including the 3 deaths) developed complications of which there were 5 cases of pneumonia, 2 of otitis media and 2 of parotitis.

The seasonal incidence of spotted fever corresponds to the tick seasons of the locality concerned. Of the 36 cases, all living in the greater Washing-

ton area, there was one case in March, one in April, 10 in May, 10 in June, 11 in July and 3 in August. Dermacentor variablis in the East appears in March and is most abundant from May to July, but it is reported that they are found as late as November and December. The history of tick bite was elicited in 69% of these patients and was not considered mandatory for a provisional diagnosis.

The majority of patients were ill for about a week prior to hospitalization. During the prodromal stage, malaise, chilly sensations and anorexia were common complaints. The invasive stage was accompanied by variable degrees of prostration, headache, irritability, muscular aches, abdominal pain, vomiting, epistaxis, photophobia, lethargy, meningismus and rarely by delirium and/or coma. In one instance there was edema of the face, feet and genitals. The spleen was palpable in 25% of cases.

In the usual instance the temperature rose rapidly to 102° to 104° in the first 2-3 days and remained elevated during the next 10-14 days; thereafter the fever came down by lysis during the third week so that a normal temperature was reached on an average of 18 days after the onset of the disease.

The rash usually appeared about the third or fourth day after the onset of fever although on occasion its appearance was delayed until the 6th or 7th day. The eruption appeared first on the extremities and back and rapidly became generalized in centripetal fashion. At first it was in the form of rose colored elevated macules, palpable and disappearing on pressure. These macules soon became deep red or purplish in color and increased in size, often becoming confluent; within a few days the rash usually became petechial in character. Cutaneous and subcutaneous hemorrhages of considerable size occurred in 40% (severe cases). In the less severe cases the petechiae remained small and discrete to give a mottling "turkey egg" effect. The rash tended to disappear with the subsidence of the fever.

The laboratory findings were not impressive and offered little help initially. The urine was that of any febrile disease. In the uncomplicated cases there was a slight leucocytosis ranging between 8 and 12 thousand with a moderate shift to the left of the polymorphonuclear elements. In 2 cases the white blood counts were 25 and 30 thousand on admission. No initial leucopenias were found. The red cells decreased in number as the disease progressed and transfusions of whole blood or plasma were required in 17% of cases.

The Weil-Felix reaction was of considerable value in establishing a diagnosis, but the time relationship for positivity only served to emphasize that the diagnosis was essentially clinical during the most critical stage of

the disease.   The earliest positive agglutination in this series was 6 days after the onset of fever; in 34 out of 36 cases, however, the OX19 aggluti- nation titer was below 1:160 before the 12th day.   In all cases but one the titer was diagnostic (i.e. above 1/160) between the third and fourth week. Titers of 1:5120 were not unusual.   One case was hospitalized on the 2nd day of fever and discharged on the 12th hospital day, the Weil-Felix reaction being negative at this time.   The patient returned to the out patient clinic as requested 22 days after the onset of fever, at which time the agglutination titer was found positive in the dilution 1:640.   It is well to point out that the Weil-Felix may be delayed until early convalescence.

The complement-fixation test with antigen from the yolk sac of the chick embryo was performed in six cases and was positive in all at the beginning of the third week.   The Children's Hospital was fortunate in having readily available the facilities of the National Institute of Health for such a specific test.

Spinal punctures were performed on 12 or 33% of these patients because of variable central nervous system signs and symptoms.   Of these, 5 showed a pleocytosis ranging between 19 and 75 cells.   Spinal fluid chemis- tries were normal.

Rocky Mountain spotted fever was considered as one of the diagnostic possibilities in 35 of the 36 cases on admission to the hospital.   This is in keeping with the premise that in an area such as ours where there is an unusual geographic concentration of the disease and where the physician is on the alert for its appearance during the tick season, the diagnosis is usually readily made clinically after the appearance of the rash.   Other diagnoses which were entertained included typhoid and typhus fever, measles and meningococcus meningitis.   Blood cultures, Widals and spinal punctures aided in the differential diagnosis.   The outstanding clinical difference was found to be the evolution and distribution of the rash.

MANAGEMENT

Prior to the use of para-amino benzoic acid the treatment was largely symptomatic and supportive.   Eght cases, prior to 1946, received hyper- immune rabbit serum developed by Topping; none of the 8 received serum during the first 3 days of the disease and none had any perceptible dimi- nution in the severity of their course.   Serum sickness occurred in 2 of the patients.   "Immune" blood was tried in one severe case but the patient died.   Because of the endarteritis in this disease, intravenous fluids have been thought to be contraindicated[3] until recently when Harrell et al.[4] demonstrated that no ill effects were noted when it became necessary to treat peripheral shock or hypoproteinemia by the intravenous route.   Our

results are essentially in agreement with their conclusions; no untoward
reactions were observed following the administration of blood, plasma,
amigen or crystalloid fluids by the intravenous route in the 9 cases where
it was employed.

USE OF PARA-AMINO BENZOIC ACID

In view of the preliminary evidence that para-amino benzoic acid might
be a valuable therapeutic agent in the treatment of rickettsial diseases,
it was deemed of considerable interest to attempt to treat Rocky Mountain
spotted fever at Children's Hospital in 1946 with this drug.

The deleterious effects observed following the use of sulfonamide drugs
in rickettsial infections led Snyder, Maier and Anderson[5] to the conclusion
that the antagonism between sulfonamide drugs and para-amino benzoic
acid in bacterial growth might be present in a reverse direction in rickettsial
infections, and prompted the investigation of the possible virtues of para-
amino benzoic acid against rickettsiae. These authors found that the
mortality from experimentally induced murine typhus in mice was con-
siderably reduced when para-amino benzoic acid was administered. In
their series, 80% of untreated control mice died while 80% of the mice who
received para-amino benzoic acid survived. Similarly, the inhibitory
effects of para-amino benzoic acid in developing chick embryos infected
with murine typhus was noted by Hamilton, Plotz and Smadel[6]. In the
first clinical investigation Yeomans et al.[7] treated 20 cases of louse borne
typhus with para-amino benzoic acid in Cairo, Egypt and used alternate
patients as controls; the daily dose of the drug ranged between 24 and 28
grams and an attempt was made to attain a blood level ranging between
10–20 mgm%. These investigators noted that the average duration of
fever for the 44 untreated cases was 18.5 days whereas in 20 cases treated
with para-amino benzoic acid the average duration of fever was 12.5 days.
In commenting on their results, Yeomans et al. pointed out that among the
group of 44 untreated cases there was only one mild case and that the fatal
cases were 18% of the total, while on the other hand there were 11 mild
cases and no deaths in the group who received para-amino benzoic acid.
The average duration of hospital stay for the treated cases numbered
21 days while that of the untreated cases was 32. These authors concluded
that para-amino benzoic acid lessens the severity of louse borne typhus
and emphasized that early initiation of therapy, preferably before the
third day, was extremely important.

The extension of clinical and experimental investigation to determine
whether para-amino benzoic acid exerted any rickettsiostatic activity
against other types of rickettsia constituted a logical extension of this field
of investigation. Tierney[8] treated 18 cases of Tsutsugamushi disease

with para-amino benzoic acid and used 16 alternate cases as controls.   He reported that the great majority of these cases receiving para-amino benzoic acid had mild courses and there were no deaths in this group; of the untreated group, however, 3 died and 7 were critically ill.   Tierney concluded that para-amino benzoic acid exerted a beneficial effect on the course of Tsutsugamushi disease and similarly emphasized the importance of early treatment, i.e. before the first week.

Smith[9], employing a dose of 2 grams every 2 hours, treated 29 cases of endemic typhus and used 29 other cases as controls; the two groups were thought to be roughly comparable on admission.   There was one fatality in each series and this author concluded that patients who received para-amino benzoic acid progressed more favorably and followed a more benign course than the untreated cases.   The duration of fever in the treated cases was 10.3 days while that in the untreated cases was 13.2 days.

Regarding the anti-rickettsial activity of para-amino benzoic acid in Rocky Mountain spotted fever, Anigstein and Bader[10] in 1945 demonstrated that when guinea pigs were experimentally innoculated with spotted fever, about 80% of these animals receiving para-amino benzoic acid inhibited spotted fever rickettsia in developing chick embryos to an even greater extent than murine typhus.   In the first reported instance of the treatment of Rocky Mountain spotted fever in humans with para-amino benzoic acid, Rose et al.[12] discuss its use in a 46 year old woman; the drug was instituted on the 5th day of the disease in a dose of 4 gms. initially and 2 gms. every 2 hours thereafter.   A prompt recovery ensued.   The para-amino benzoic acid blood levels in this case ranged between 6.6 and 18.6 mgm%.

During the summer of 1946 all 6 cases of Rocky Mountain spotted fever diagnosed at Children's Hospital had been treated with para-amino benzoic acid.   Ideally it would have been desirable to have treated alternate cases with this drug employing the untreated cases as controls.   However, the number of cases were too few to allow any such control series.   Two additional cases in adults were treated by one of us (P. A. M.) and will also be described.

Powdered para-amino benzoic acid was partially dissolved in 5% bicarbonate of soda solution so that 15 cc. of the mixture contained one gram of para-amino benzoic acid.   This preliminary neutralization lessened gastric irritation and the drug was well tolerated by the patients.

Three representative cases follow.   The other five cases are discussed in detail in the original article in the Journal of Pediatrics.

Case 1.   D. B., a 4 year old white female, was admitted to Children's Hospital on July 29, 1946 with the complaints of malaise and fever for 7 days duration and a rash of 5 days duration.

The child had been perfectly well until one week prior to entry at which time she was noted to have become listless and feverish.   Forty-eight hours after the onset of the fever a rash appeared which had its initial distribution about the feet and ankles and progressed so that during the next 2 or 3 days there was a generalized distribution over the trunk, chest and upper extremities.   Concomitantly the child complained of headache and muscular aches and pains in the upper and lower extremities and experienced considerable malaise.   The appetite was poor and the child vomited on one occasion.   The temperature remained elevated during the entire week prior to entry and the child during this interval appeared acutely ill.

The patient resided on a farm near Potomac Mills, Virginia.   Ticks had been noted in this area and during the earlier part of the spring had been observed on the child and removed but none had been noted recently.

The past history and family history were non-contributory to the present illness.

Physical examination at the time of entry revealed a well developed, well nourished 4 year old white girl who appeared acutely ill but in no obvious distress.   Her temperature was 104.8°, the pulse rate 140, and the respiratory rate 40.   Her sensorium was clear but she appeared very irritable and was uncooperative.   A discrete, maculopapular rash which blanched on pressure was noted chiefly on the upper and lower extremities and the trunk. There were a few scattered lesions on the palms and soles.   No ticks were found in the hairy regions.   The posterior cervical, axillary and inguinal nodes were small and shotty.   The neck was supple and Kernigs and Brudzinski signs were negative.   The heart and lungs were normal.   The liver and spleen were not palpable.   The motor and sensory modalities were in good order.   Physical examination was otherwise negative.

In view of the clinical findings together with the known concentration of ticks in this area, a provisional diagnosis of Rocky Mountain spotted fever was made.

Laboratory examination revealed a hemoglobin of 10 gms. with 3.5 million red cells; the white cell count was 8400 with 55% neutrophiles, and 45% lymphocytes.   The urinalysis was essentially negative.   Blood culture was negative as was the Wasserman and Kahn.   Weil-Felix agglutination test with Proteus OX19 on July 29, eight days after the onset of illness, was positive in a dilution of 1:20.   Five days later the titer had risen to 1:640.

Throughout the first 2 days in the hospital the child remained acutely ill with the temperature spiking between 100° and 104.5°.   Drowsiness and irritability were marked and the child's appetite remained poor.   The rash which had become more petechial now involved the entire thorax and abdomen.   During this time supportive measures including antipyretics and an intravenous infusion of 300 ccm. of 5% glucose in saline were administered.

On July 31, 48 hours after admission, para-amino benzoic acid therapy was started.   The dose was 3 gms. initially and then $1\frac{1}{2}$ gm. every 2 hours thereafter.   On the following day, the dose of para-amino benzoic acid was reduced to 1 gm. every 2 hours and this dosage was maintained throughout the remainder of therapy.   Frequent para-amino benzoic acid blood levels were taken one hour following the previous dose and revealed the blood level to range between 16 and 24 mgm% (Chart 1).

DAY OF ILLNESS	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25

DB.♀
4 YRS.

TEMP. (°): 105, 104, 103, 102, 101, 100, 99, 98.6 — temperature spikes between 103–105 early, then drops rapidly to normal around day 16–17 and remains normal.

| PABA LEVEL MGM % | 16 | 20 | 24 | 18 |

| WEIL-FELIX | $\frac{1}{20}$ | $\frac{1}{320}$ | $\frac{1}{640}$ |

| WBC | 8400 | 7800 | 4100 | 9000 | 4600 | 3600 | 4500 | 4600 | 5300 |

| % PMN | 55 | 58 | 54 | 46 | 16 | 16 | 25 | 41 | 30 |

| PROTHROMBIN % NORMAL | 50% | 70% |

| CEPH. FLOCC'N | 4+ |
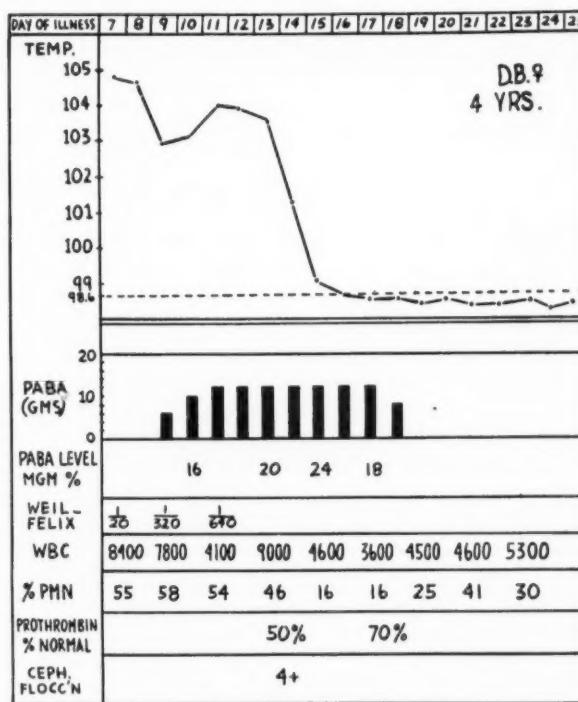
CHART 1

Two days following initiation of para-amino benzoic acid therapy a rather definite improvement was noted.   The patient appeared less toxic, was considerably more alert and her appetite improved.   However, the temperature continued to spike during the next 5 days ranging between 100° and 102°.   On the 6th day of para-amino benzoic acid therapy the temperature dropped rapidly to normal.   By this time the rash had already begun to fade and the patient was asymptomatic.   The child remained afebrile dur-

ing the remainder of her hospital course. Her recovery was complete and she was discharged on the 17th hospital day after an uneventful convalescence.

Para-amino benzoic acid had been administered for 10 days during which time the child received a total of 110 grams.

Daily white counts obtained during the course of drug therapy to determine its leukopenic effect revealed a definite granulocytopenia and leukopenia one week after the initiation of para-amino benzoic acid therapy; the white count at this time was 3500 with 16% neutrophiles. However, the white count rapidly returned to normal when the para-amino benzoic acid was discontinued. Hepatic function tests obtained during the course of para-amino benzoic acid therapy showed a prothrombin time of 50% of normal, total protein of 6.9 gms.% and a 4 plus cephalin flocculation test.

Case 3. D. V., a 16 month old white female, was admitted to Children's Hospital on August 8, 1946 with a history of a tick bite 6 days prior to admission. The child seemed well until one day before entry at which time she appeared irritable and fever was observed. On the day of admission a maculo-papular rash was noted on the extremities and the abdomen. The past history and family history were non-contributory.

Physical examination revealed a well developed, irritable child who appeared acutely ill. A diffuse pale pink maculo-papular spotted eruption was noted over the entire body including the face and extremities. A moderate degree of conjunctivitis was noted. The liver and spleen were not palpable, and no meningismus was elicited.

Laboratory examination revealed a hemoglobin of 10 gms.; the white cell count was 10,600 with 58% neutrophils, 38% lymphocytes and 4% monocytes. The urine was negative and the blood culture was sterile. The Weil-Felix agglutination test with proteus OX19 on August 9th, 3 days after the onset of the illness, was negative; 8 days later the titer had risen to 1:80 and a repeat agglutination test 22 days after admission showed a titer of 1:640. The total protein was 6.5 gms.% and the prothrombin time was 70% of normal. The cephalin flocculation test 6 days after entry was 3 plus.

On the day of admission, para-amino benzoic acid therapy in a dose of 2 grams initially and one gram every 2 hours thereafter was started and this dosage was maintained throughout the remainder of therapy. The drug was continued for 8 days during which time the child received a total of 74 grams. Repeat para-amino benzoic acid blood levels obtained during therapy showed a level ranging between 20-40 mgm%.

Within 48 hours after initiation of therapy the temperature dropped precipitously to normal and the child remained afebrile during the remainerd

of her hospital stay (Chart 3).   Coincident with the drop in temperature the patient's clinical improvement was noteworthy and the rash began to fade on the 5th hospital day.   The child was discharged on the 12th day after an uneventful convalescence.

A slight leukopenic effect was observed on the 7th day of therapy, the white cells dropping to 5700 with 25% polys; the white count promptly rose to 9600 two days following termination of therapy.

DATE	8/8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
DAY OF ILLNESS	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
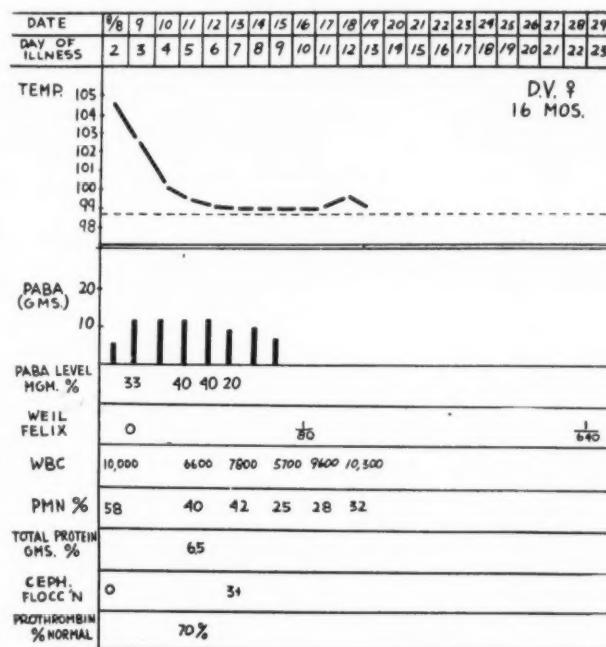
CHART 3

Case 5.   J. L. M., a 4 year old white male, was admitted to the hospital on the 8th day after the onset of his illness.   The temperature on admission was 104.5° and the child appeared quite toxic and dehydrated.   There was a diffuse petechial rash covering the extremities and trunk.   A clinical diagnosis of Rocky Mountain spotted fever was made and subsequently confirmed by a Weil-Felix agglutination titer of 1/2560.

Para-amino benzoic acid therapy was begun on the day of admission with

an initial dose of 3 grams and $1\frac{1}{2}$ grams every 3 hours thereafter. Some improvement was noted during the next 3 days while on therapy, the temperature dropping to normal during this interval. However, on the 4th hospital day, the patient became mildly incoherent and confused and a moderate degree of periorbital and peripheral edema was observed. Concomitantly the temperature again rose and the child appeared definitely worse The para-amino benzoic acid blood level ranged between 53–80 mgm% at this time, and because of the uncertainty regarding the possible toxic effects of the drug as a contributing cause, it was discontinued. Shortly thereafter the child became comatose with evidence of peripheral shock. On the 8th hospital day, a bilateral parotid swelling was observed; at this time a history of possible exposure to mumps 2 weeks prior to entry was elicited from the parents. A spinal tap was performed on the following day and was negative. Two days later, definite evidence of the right lower lobe pneumonia was demonstrable both on physical examination and on x-ray.

The patient's condition remained critical during the next few days during which time the temperature fluctuated between 102–104°, and the rash became markedly hemorrhagic and diffuse. Supportive therapy consisted of penicillin, oxygen and intravenous infusions of crystalloids and blood. Improvement was gradual but progressive and the temperature came down by lysis during the course of the next 2 weeks. The child was discharged on the 32nd hospital day after a complete recovery.

No leukopenic effect was observed during the time para-amino benzoic acid was administered.

<div align="center">COMMENT</div>

Our results with para-amino benzoic acid in Rocky Mountain spotted fever were in effect similar to those obtained by Yeomans[7], Tierney[8] and Smith[9] against louse borne typhus, scrub typhus and murine typhus respectively. The improvement was more gradual than dramatic and the temperature came down by lysis over the course of several days with concomitant improvement clinically. The morbidity, duration of the disease and degree of toxicity seemed to be modified to a greater or lesser extent in 6 of the 8 cases treated with para-amino benzoic acid as compared to the 30 untreated cases observed during the previous 15 years in Children's Hospital. The mortality rate among the untreated group was 10% (3 deaths in 30 cases) while in the 8 cases managed with para-amino benzoic acid there were no deaths. Admittedly, the latter series is too small to permit any significant statistical evalution and only further extensive clinical trials will allow any definite conclusions regarding the efficacy of para-amino benzoic acid in Rocky Mountain spotted fever. The evidence thus

far is suggestive but not conclusive. The response to para-amino benzoic acid was in no way comparable to the dramatic response of susceptible bacterial infections to sulfonamides and antibiotic drugs. Had therapy been started earlier in these cases, it is possible that a more prompt response might have been observed.

Mode of Action of Para-Amino Benzoic Acid: The important role assumed by para-amino benzoic acid in the metabolism of bacteria which multiply out side the cells of the body has been clarified since the advent of sulfona-midedrugs; the antagonism between the latter and para-amino benzoic acid is now well known. However, rickettsias reside and multiply intracellularly, largely within the endothelial cells of small blood vessels. Para-amino benzoic acid theoretically must gain access to the organisms located within the cell and, in a manner which is as yet strictly speculative, inhibit the intracellular multiplication of the rickettsia, possibly by virtue of stimulation of the metabolism of the host cells. Grieff, Pinkerton and Moragues[14] hypothesize that either the high metabolic activity of para-amino benzoic acid on the enzyme system produces an unfavorable milieu for the multiplication of rickettsia within the cell or that enzymes necessary for the growth of rickettsia disappear from the host cells. This would be in keeping with a rickettsiostatic rather than a rickettsiacidal mode of action. That para-amino benzoic acid does not act directly on the multiplication of rickettsia is inferred from an experiment in which the organisms were exposed to a concentration of 50 mgm% of para-amino benzoic acid without affecting their virulence for animals.[11] Anigstein and Bader[13] have demonstrated that pathological lesions typical of spotted fever including a large friable spleen and pneumonitis developed in infected guinea pigs even though para-amino benzoic acid had been administered; they further demonstrated that when the spleen from such animals was injected into susceptible guinea pigs, there resulted a fatal spotted fever infection. In the opinion of these authors the conclusion seemed warranted that para-amino benzoic acid produces its effect by suppressive rather than destructive action on rickettsiae.

Time of Initiation of Para-Amino Benzoic Acid as Related to the Response to Therapy: It is generally agreed that the earlier para-amino benzoic acid therapy is initiated, the better the rickettsiostatic response. In guinea pigs experimentally innoculated with a highly virulent strain of Rocky Mountain spotted fever, Anigstein and Bader[13] found that a progressive delay in initiating para-amino benzoic acid therapy diminished the efficacy of the drug; these authors considered a 48 hour delay as probably being borderline. Yeomans et al.[7] reported that the best results in louse borne typhus in humans were obtained when the drug was started on the 2nd and 3rd days of illness but observed some effect when the treatment was begun as late as the 7th day. Two thirds of the cases of Tsutsugamushi disease treated

by Tierney[8] received the drug not later than the 5th day and no case was started on therapy later than the 7th day of illness. In both of these well controlled series conducted under the aegis of the American Typhus Fever Commission, patients were hospitalized early and para-amino benzoic acid therapy was begun shortly thereafter. However, early hospitalization (i.e. within 2–3 days after onset of fever) is not the rule in sporadic cases of tick fever in civilian practice. Only 3 of the 8 para-amino benzoic acid treated cases in this series were hospitalized prior to the 4th day while the other 5 patients were admitted within the 7th to the 10th day after the onset of illness. Of these, only one patient (case 3) was started on therapy prior to the 6th day. Any attempt to evaluate the time of initiation of therapy as related to the duration of the disease as judged by our results would necessarily be invalid because of the small number of cases in our series. Unquestionably case 3 who was started on therapy two days after the onset of the disease showed the most striking response with the temperature returning to normal within two days after the initiation of para-amino benzoic acid therapy. In 5 other cases where para-amino benzoic acid therapy was begun within 6–10 days after the onset of the disease, the response to therapy was encouraging but not remarkable, with the temperature coming down to normal within an average of 6 days after initiation of the drug. In the remaining 2 cases (case 5 and 6) both of whom began to receive para-amino benzoic acid 8 days after the onset of the disease, any accurate evaluation of the efficacy of para-amino benzoic acid therapy was difficult. Both of these patients represented severe examples of tick fever and followed strikingly parallel courses. In case 5, the drug was discontinued prematurely on the 4th day and a progressive change for the worse in the child's condition occurred, either by coincidence or otherwise, shortly thereafter; the picture was further complicated by a superimposed parotitis and bronchopneumonia. Similarly case 6 was complicated by bronchopneumonia and parotitis (due to mumps) as well as mumps meningo-encephalitis. These superimposed infections serve to vitiate any attempt to appraise the effect of para-amino benzoic acid in both cases. It is worth noting that both children were delirious and comatose at a time when the para-amino benzoic acid blood levels ranged between 40–80 mgm%. At the time, it was considered that the marked lethargy and disorientation noted in both children could have been due to any one of three causes, viz. that due to severe tick fever per se, that due to the toxic effects of the drug and thirdly (in case 6) that ascribable to the complicating mumps meningoencephalitis. As will be discussed later, the studies on ingestion of large doses of para-amino benzoic acid in a series of 6 normal children who served as controls would make it appear that the drug was a less likely contributing factor.

As Yeomans et al. [7] have stated, it is apparent that a much wider clinical trial with para-amino benzoic acid in rickettsial diseases would be required before it would be possible to determine the limits within which salutary effects with the drug may be expected.

Toxicity of Para-Amino Benzoic Acid: A definite leukopenia and granulocytopenia was found in only one of the 8 cases treated with para-amino benzoic acid. In this patient (case 1) the white cell count went down to 3,600 with 16% polys on the 9th day of therapy and rose within 4-5 days following discontinuation of drug therapy. In one other instance (case 6) a white cell count of 4,700 with 57% polys was noted. No definite correlation was observed between the degree of leukopenia and the para-amino benzoic acid blood level. It is generally agreed [7, 8, 9] that if a leukopenia under 3,000 is observed, it is advisable to discontinue para-amino benzoic acid therapy. The importance of performing daily white blood cell counts while the drug is being administered is apparent. No change was observed in the red cell count and hemoglobin.

There is no evidence thus far that para-amino benzoic acid produces any kidney complications in a fashion similar to sulfonamide drugs which in their chemical configuration are related to para-amino benzoic acid. A good urinary output was initiated in para-amino benzoic acid treated cases to forestall the possibility of producing excessively high blood levels.

In 5 of the 8 cases of spotted fever where para-amino benzoic acid was employed, cephalin flocculation tests were obtained within 12 to 19 days after the onset of the disease (or within 5 to 12 days after therapy was initiated) and in all 5 cases a positive cephalin flocculation ranging between 3 and 4 plus were noted. In view of the fact that tick fever per se is capable of producing a pronounced reduction in liver function there was some question whether the evidence of liver damage presented in these cases represented a dysfunction due to the disease or para-amino benzoic acid or both.

In an attempt to evaluate this point a series of 4 controls selected at random from the wards, ranging in age between 3 and 11 years, were given one third of a gram of para-amino benzoic acid per pound of body weight in 24 hours in a 3 hour divided dosage schedule for 4 consecutive days and daily cephalin flocculation tests were obtained. In two instances the cephalin flocculation rose from 0 to 3 and 4 plus within 24 to 48 hours after the initiation of para-amino benzoic acid. In the other 2 cases the cephalin flocculation increased from a control 2 plus to 4 plus within the same interval (Table 1).

In a similar group of six controls receiving the same dose of para-amino benzoic acid, daily prothrombin time determinations were obtained. It was found that the prothrombin level dropped gradually from an initial average of 109% to 77% of normalcy within 4 days. The results obtained

in this control group are suggestive but by no means conclusive that para-amino benzoic acid may exert some untoward effect on liver function. Further control studies, however, would be indicated before any categorical statement could be made. It might be well to add that in view of the fact that para-amino benzoic acid is largely conjugated with glycine by the liver to produce para-amino hippuric acid, the possible dangers of administering the drug in the presence of a liver already damaged by spotted fever also requires further clarification.

DAYS AFTER PABA STARTED	MGS. % PABA	PLATELETS	PROTHROMBIN % NORMALCY	CEPHALIN* FLOCCULATION	CABON DIOXIDE COMBINING POWER
1	15	319,000	109	0 to 4+	
2	26	352,000	103	3+ to 4+	
3	32	347,000	99	3+ to 4+	
4	37	240,000	77	3+ to 4+	36
PABA discontinued					
6					45

* Cephalin flocculation tests obtained prior to the administration of PABA were negative in two cases and 2+ in two others.

TABLE 1

SUMMARY OF A CONTROL GROUP OF SIX NORMAL CHILDREN SELECTED AT RANDOM FROM THE WARD WHO RECEIVED ½ GRAM OF PABA PER POUND OF BODY WEIGHT PER 24 HOURS IN A 3 HOUR DIVIDED DOSAGE SCHEDULE FOR 4 CONSECUTIVE DAYS

PABA levels, platelet counts and prothrombin determinations were obtained daily on each of the six children while the cephalin flocculation tests were obtained daily on 4. The CO_2 combining power was done only on the 4th and 6th day of the experiment. The average of the six daily determinations in each category are noted above.

In this regard platelet counts performed daily in the control group showed no significant reduction during the 4 day period that para-amino benzoic acid was administered.

Carbon dioxide combining powers were also obtained in each of 6 cases in this control series on the 4th day of drug ingestion (Table 1). Levels ranging from 28 to 44 volumes % with an average of 36 volumes % were noted. No acidotic dyspnea was noted. Two days after discontinuing para-amino benzoic acid administration the CO_2 combining power rose in all cases but one to levels ranging between 40 and 52 volumes %. This reduction of CO_2 combining power ensued in spite of preliminary neutralization with 5% sodium bicarbonate which was designed to lessen gastric irritation. Although this control series is small it would seem that para-amino

benzoic acid is capable of producing a moderate transient reduction of CO_2 combining power and it is suggested that CO_2 combining power determinations be obtained periodically when the drug is employed to avoid any complicating acidosis.   The mechanism of this imposed disturbance in acid base balance is not clear.

In spite of the relatively high drug levels (up to 54 mgm%) attained in this control group, no evidence of drowsiness or lethargy was observed. This serves to suggest that the apathy and disorientation noted in some of the para-amino benzoic acid treated cases (especially 5 and 6) may have been due to the disease rather than the drug.   It should be borne in mind, however, that in the face of the evidence noted above that para-amino benzoic acid is capable of producing a reduction of the CO_2 combining power there is the possibility that drowsiness and even coma *can* result from para-amino benzoic acid if severe acidosis supervenes.

Optimal Dose: The optimal dose of para-amino benzoic acid requires further experimental and clinical experience. The drug is excreted rapidly in the urine so that at the end of 2-3 hours only minimal amounts are still detectable in the blood.   Hence frequent administration of the drug, preferably on a 2 hour dosage schedule, is indicated.   Yeomans et al.[7] administered 24 to 28 grams of para-amino benzoic acid orally per day (usually 2 grams every 2 hours) to adults with louse borne typhus and considered 10-20 mgm% to be an adequate blood concentration.   Smith[9] used a similar dosage schedule in the management of 29 cases of murine typhus. In Tierney's[8] series of Tsutsugamushi disease, para-amino benzoic acid was administered in a dosage of 8 grams initially and then 3 grams every 2 hours; on this regimen, blood concentrations of 30-60 mgm% were achieved within 2 days and in some cases a blood level ranging between 95-150 mgm% was attained.   Tierney[4] cites one case where an acutely ill patient had 2 convulsive siezures at a time when he had a para-amino benzoic acid blood level of 103 mgm%; however, these convulsions were thought to have been due to the disease rather than to the drug.   There is no definite evidence thus far that such inordinately high doses are necessarily more efficacious than lower doses in Rocky Mountain spotted fever and until more is known regarding the possible untoward reactions of para-amino benzoic acid it is probably the better part of discretion to attempt to maintain a blood level between 20-40 mgm%.   In our series of 6 cases of tick fever in children ranging in weights from 20-80 lbs. we found that one third to one half a gram per pound of body weight per 24 hours in a 2 hour divided dosage schedule would usually yield a para-amino benzoic acid blood level ranging between 15-40 mgm%.   This was confirmed in a control series of 6 normal children (see Table 1).   It is well to add that in the control series, a hiatus of 24 to 48 hours was required to attain the higher levels ranging

between 25 to 40 mgm% suggesting that a cumulative process was operative. In agreement with Tierney[8], we found a considerable variation from patient to patient in blood levels attained with comparable doses. The desirability of performing daily blood levels during therapy is apparent. In our cases the para-amino benzoic acid blood levels were routinely obtained one hour after the previously administered dose of the drug; this permitted a more uniform evaluation of the level in view of the rapid excretion of para-amino benzoic acid within 2 to 3 hours after administration.

The optimal duration of therapy again is arbitrary pending further clinical trials. In our series, therapy was maintained for an average of 7 days and was usually discontinued within 2–4 days after the temperature returned to normal.

<div align="center">CONCLUSIONS</div>

1. A review of 38 cases of Rocky Mountain spotted fever (36 of which were seen at Children's Hospital) from 1931 to 1946 is presented.

2. In the 8 cases of tick fever treated with para-amino benzoic acid during the summer of 1946 (6 children and 2 adults) it would appear that the degree of toxicity, duration of the disease and morbidity were favorably modified to some extent when compared to the 30 untreated cases observed during previous years. The mortality rate in the untreated group was 10% while there were no deaths in the 8 cases managed with para-amino benzoic acid.

3. Administration of one third of a gram of para-amino benzoic acid per pound of body weight in 24 hours in a 2 hour divided dosage schedule over a period of 4 days to 6 normal children in a preliminary control experiment suggested the following conclusions:

   a. Para-amino benzoic acid blood levels ranging between 15–36% could be maintained with this dose.

   b. Daily prothrombin time determinations and cephalin flocculation tests showed changes suggestive of transient liver dysfunction.

   c. The CO_2 combining power was also moderately reduced temporarily by the drug.

4. The following standard order procedure has been adopted at Children's Hospital for the management of cases of tick fever during the current season.

I. Laboratory Work-Up

   a. Daily WBC and differential. (Discontinue PABA if WBC goes below 3000)

   b. Daily PABA level (obtain one hour before next dose)

   c. Urine and NPN every second day.

   d. Cephalin flocculation, prothrombin time, CO_2 cp. and total protein before therapy is started and every 3rd day thereafter.

e. Weil-Felix and Complement Fixation as indicated for diagnosis.

f. Intake-output charts on all patients.

II. Treatment

   a. PABA

      1. To make a solution containing one gram of PABA per 15 cc: Add 15 gms. Bicarbonate of Soda to 300 cc of water; then add 20 gms. PABA *slowly* to this 5% solution of Bicarbonate of Soda. Keep in icebox on the ward and serve chilled. It may be necessary to gavage the solution in semi-comatose cases. Disguise taste of solution with fruit juice, etc. in young patients if necessary.

      2. Dosage: Approximately $\frac{1}{3}$ to $\frac{1}{2}$ gm. per lb./24 hrs. will often suffice in a 2 hour divided dosage schedule. However, the dose may have to be varied somewhat to maintain a suggested optimal PABA blood level ranging between 20–40 mgm%.

      3. Duration of therapy: Usually between 3–5 days after temperature returns to normal.

   b. Intravenous Fluids

      Plasma, crystalloids, amigen and blood and parenteral vitamins as needed. Observe closely for hypoproteinemia and acidosis.

   c. Diet

      High carbohydrate and protein, low fat diet as tolerated. Urge liquids orally.

   d. Complications

      Pneumonitis—penicillin is drug of choice. Sulfonamides contraindicated. Congestive Failure—digitalis

ADDENDA

Since this paper was written, three additional cases of tick fever have been treated with para-amino benzoic acid during the summer of 1947. In all three cases, rather rapid improvement ensued following initiation of therapy with the temperatures returning to normal within 2 to 3 days. The duration of the disease prior to hospitalization ranged between 5 to 7 days.

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ENCEPHALITIS OR TETANUS?

Case Report No. 102

Charles Steigler, M.D.   M. B. 47-2487

M. B., a 2½ year old colored female, was admitted to this hospital on
March 14th because of "choking spells." She was apparently well until
the morning of March 13th at which time she had difficulty swallowing
some orange juice, choked and "became unconscious for about 10 minutes."
Upon regaining consciousness, the child seemed well until several hours
later when she had another choking spell while trying to drink some fruit
juice, but she did not lose consciousness at this time. She was brought to
the hospital dispensary where a diagnosis of upper respiratory infection
was made and symptomatic therapy was prescribed. At home that evening,
the patient had a third choking spell while attempting to drink water;
during this spell she gritted her teeth and her body became stiff for several
minutes, but she did not lose consciousness. At 2:00 A.M. on March
14th, while trying to give the patient the medicine prescribed in the out-pa-
tient department, the parents stated she had an attack similar to that
of the preceding evening, but at this time she was unconscious for about
10 minutes. The morning of admission to the hospital, she complained
of pains in her back and abdomen, but there were no associated symp-
toms referable to the gastrointestinal or genitourinary systems. The past
history was unrevealing except for the fact that the patient had received
no immunizations. The family history was non-contributory, and there
was no history of any injury or animal bite.

Physical examination on admission revealed an acutely ill, well nourished,
well developed 2½ year old colored female, not appearing acutely ill, sitting
up in bed and talking freely. The lips were dry and cracked, and the breath
was malodorous. The tongue was dry, clean and slightly furrowed. At-
tempts to visualize the pharynx were met with marked resistance, part of
which was voluntary; when talking or when offered fluids, the patient
opened her mouth about half way without noticeable difficulty. She was
unable to swallow completely the fluids offered, but would choke and gag,
after which a small amount was swallowed; the remainder drooled from her
mouth and a smaller amount regurgitated through her nose. Because of
the possibility of a retropharyngeal abscess, the pharynx was visualized
under light anesthesia; no abnormalities were noted. The entire abdominal
wall was resistant on examination, but without evidence of tenderness,
masses or enlarged viscera. There was no evidence of meningeal irritation;
the patient sat up easily and the gait was normal. There were no other

findings of note on physical examination except for a mild dehydration.
The temperature was 102.2° (R), the pulse rate 140 beats per minute, the
respiratory rate 30 per minute.

A hemogram on admission showed 12.5 gm. hemoglobin, 4,350,000 eryth-
rocytes and 13,200 leucocytes, of which 83% were neutrophiles; there was
no shift to the left. Urinalysis and spinal fluid examination were normal.
Smears of the tonsils and pharynx did not reveal any polar staining bacilli.
Radiographic examination of the chest and pharynx revealed no abnor-
malities.

During the first 24 hour period of hospitalization, increasing spasticity
of the extremities and a tendency to lie in opisthotonous were noted. Marked
nuchal rigidity appeared, and trismus was present. It was decided to treat
the patient as a case of tetanus; accordingly, she was given 300,000 units
of tetanus antitoxin intramuscularly during the following 36 hours. Peni-
cillin therapy, which had been instituted on admission, was increased to
100,000 units intramuscularly every 2 hours because of the patient's critical
condition. Lumbar puncture was repeated on March 16th; there were 11
leucocytes per cubic mm. of spinal fluid of which 30% were polymorphonu-
clears and 70% were lymphocytes; no organisms were grown on culture.
Successive hemograms during the first hospital week showed a tendency to
a slight leucopenia with a normal differential count. Successive urinalysis
showed a mild albuminuria, occasional casts and white blood cells, but no
other abnormalities. Three consecutive blood cultures yielded no growths.
On March 16th the serum calcium level was 6.8 mgm% and phosphorus 3.3
mgm%. The patient was given 10 cc. of 10% calcium gluconate intra-
venously on March 17th and March 20th without any improvement in the
clinical picture, although subsequent serum calcium levels were normal.

On March 18th, it was noted that she had a left facial weakness. Al-
though all extremities were spastic, the spasticity was more pronounced on
the left side. The trismus and the abdominal muscle spasm persisted but
the significance of these findings were controversial; some observers believed
it was largely voluntary, while others did not. The sensorium was intact.
When the patient was asleep the spasticity of the extremities and the ab-
dominal wall and the trismus was not present. Throughout this period,
the patient was unable to take fluids orally without choking and gagging;
fluid intake was maintained by the administration of parenteral fluids. She
was irritable, and would become opisthotonic when examined, but other
stimuli (i.e. noise and light) did not produce this effect. Lumbar puncture
was repeated on March 17th and 21st. On both examinations of the spinal
fluid the protein, sugar, cell count and chloride were within normal limits;
the colloidal gold curve and Wassermann were negative. Blood serology
was negative and the blood non-protein nitrogen level was normal on two

occasions. Radiographic examination of the skull revealed no abnormalities.

The clinical picture continued without any great change throughout the ensuing 3 weeks. The temperature course throughout this period ranged between 99°–102° (R), and was not characteristic of any specific infectious entity. During the 3rd week of her illness, the patient began to take small sips of fluid by mouth for the first time, but still had difficulty in swallowing and gagged frequently. There was a slow subsidence of the spasticity, facial weakness and difficulty in swallowing during the 4th and 5th weeks of her hospital stay.

A lumbar puncture on April 7th revealed normal spinal fluid, and an agglutination test with febrile antigens was negative at this time.

Penicillin therapy, which had been reduced to 300,000 units in oil and beeswax once daily on March 24th was discontinued after two weeks.

The patient was discharged on April 24th and no residuals were present.

DISCUSSION

Vasilios Lambros, M.D.: From the beginning this case was a most perplexing and puzzling one as it did not fall into a pattern suggestive of any recognizable disease entity. However, the two most likely disease processes that could cause a picture such as this were tetanus and encephalitis.

The factors that draw me away from the diagnosis of tetanus are as follows:

1. The absence of any history of an injury or open wound within the past three months. (It should be called to mind that only in approximately 65% of cases of tetanus will you find a history of an open wound.)

2. The presence of so-called mesencencephalic convulsions in the first 24 hours of the disease. This is never seen in tetanus, and has not been recorded by any observers.

3. The gradual appearance of extensor spasms involving the throat and all four extensors and which tended to increase with tactile stimuli. Yet it must be noted that auditory and visual stimuli did not affect the extensor spasms in any way whatsoever. It is a well known fact that cases of tetanus have to be kept in a relatively quiet and dark room lest the child be thrown into a series of convulsions.

4. A total absence of clonic convulsions or twitching which is so characteristic of this disease. In tetanus there is always either local or generalized clonic convulsions and at no time did this child exhibit this manifestation.

5. There was some spasm of the masseters and the depressors of the mandible and yet no true trismus. The dysphagia which this child

had could be explained on the spasm of throat muscles. It was my opinion that at no time did a true trismus exist.

6. The rigidity of the spinal reflex arc as found in tetanus requires heavy sedation for its release. Frequently natural sleep is not sufficient to release this spasm. With light sleep this patient's spasm would release itself.

7. On the 5th day of illness, a left lower facial weakness and an increase in the spasm of the left extremity developed. It is unheard of to find either specific cranial or cortical involvement in tetanus. This is much more characteristic of an encephalitis with involvement of the mid-brain and the higher centers.

8. The disease processes completed its evolution without any noticeable clinical effect from penicillin and tetanus antitoxin or any other medications.

In summary, at no time did this case behave or follow the pattern of tetanus in accord with observations from our previous 39 cases. Clinical impressions do not substantiate the diagnosis of tetanus and while there may be some discussion on some of the above mentioned factors, yet there are some, of major importance, in which no good refutation can be offered and which are contradictory to a diagnosis of tetanus.

The reasons for calling this an encephalitis are as follows:

1. The presence of mesocephalic involvement which indicated involve-ment of the midbrain and the higher centers.

2. The typical extensor spasm which is primarily characteristic of mid-brain involvement.

3. The development of a left lower facial weakness and an increase in the left extremity spasm.

4. The suppression of the extensor spasm with mild cortical depression.

5. The gradual progression and subsidence of the disease process without any effect of any medication which is so typical of a virus encephalitis.

This spring we have had an unusual number of bizarre encephalitic in-volvements. Some have been grouped as Von Economo's encephalitis, while others have not been classifiable. I do not like to be dogmatic about the diagnosis of encephalitis but as it is probably not tetanus the only other possibility is encephalitis of virus origin with predominant involve-ment of the midbrain.

Frederic G. Burke, M.D.: I examined this child 24 hours after admission and on several occasions during her stay in the hospital. My initial im-pression centered particularly about the presenting symptoms of trismus and generalized muscular spasm, which was quite marked. I was not impressed by any evidence of localized signs noted by several other ob-

servers.   Evidence of hemi-lateral involvement of the musculature was never clear-cut and trismus and nuchal rigidity were the two signs that were persistently present at every examination and which gradually resolved over a period of weeks.

The normal spinal fluid does not necessarily rule out "a tetanus syndrome due to encephalitis of obscure etiology" but is in far more keeping with the diagnosis of tetanus.   The lack of history of injury does not militate against this diagnosis because at least 25% of children with tetanus fail to supply a history of trauma or have any evidence of wounds upon initial examination.   The child was treated with tetanus antitoxin and appeared to respond in a typical fashion over a period of several weeks.

I believe that the burden of proof lies with the observers who would say that this child did not have tetanus and such proof is lacking.

William Burdick, M.D.: This patient when first seen by me presented a most striking picture of opisthotonus and a very marked trismus.   There was no history of a wound and no evidence of an abrasion or other source of entrance for the tetanus organisms.   The trismus was such a striking part of the picture that we decided that we could hardly, in justification, refrain from giving anti-tetanic serum.   Dr. Lambros saw the patient with me and agreed that the treatment had better be started for he was unable to give us any better diagnosis than a possible tetanus even though it did not appear to be a typical picture of this disease.

E. Clarence Rice, M.D.: The absence of any history of injury or animal bite would tend to eliminate two of the most likely diagnostic possibilities in this case, viz., tetanus and rabies.   I have never seen a patient with tetanus having as complete muscular relaxation during sleep as did this patient.   It was only when awake that the trismus and spasticity were especially noticeable.   The presence of 11 leucocytes per cubic millimeter in the spinal fluid with normal chemistry is a bit abnormal and could be compatible with a virus infection of the central nervous system.   Rabies rarely pursues such a benign course and is usually fatal.   Thorough examination of the nose and throat gave no evidence of the cause of the illness. The presence of fever and the age of the child would almost certainly rule out a purely functional condition.   The lack of response to the administration of calcium and the duration of the illness would eliminate tetany.

I believe that tetanus and rabies can be ruled out and that the illness can best be explained on the basis of a virus infection of the central nervous system, the lesions being confined to the motor areas.

Dr. William Howard: When this child was first seen on the ward, it was the writer's opinion that she was suffering from tetanus, and subsequent review of the case record would appear to strengthen this belief.   The

diagnosis of tetanus, especially in the absence of an obvious wound or injury serving as a portal of entry, must be made largely on the basis of the clinical picture. Laboratory data are helpful only in the exclusion of confusing conditions.

As in the present case, tetanus typically begins with difficulty in swallowing, muscle stiffness and muscle pain, to be followed in forty-eight hours by well defined muscle spasm, and rigidity, and the characteristic masseter spasm and facial expression. Depending upon the amount and distribution of toxin actually fixed in nerve cells, the picture and course may vary considerably. When lethal doses of toxin have been absorbed prior to the administration of antitoxin, convulsions are frequent and severe, and cyanosis and asphyxia are common. When less than a lethal dose has been absorbed, convulsions may be milder or even absent and only muscle spasm and rigidity be present, though these are usually intensified by any type of stimulation. Characteristically there is a low grade fever present throughout the active phase of the disease, which may rise sharply in the terminal stages of fatal cases.

The duration of the disease varies greatly, but in those cases that recover the improvement is gradual and full recovery may take from three to six weeks. Paralysis or weakness of facial muscles has been reported as a complication of tetanus, which usually disappears with clinical recovery from the disease. Failure to find an injury or other suitable portal of entry for the infection is too common an occurrence to require further comment.

In this case, the lack of any significant laboratory findings, especially in regard to the spinal fluid, would appear to substantiate the diagnosis of tetanus, as does the subsequent recovery.

This patient presented a fairly typical picture of tetanus of moderate severity. Her symptoms of choking, gagging, and muscle spasm are typical, as is the relaxation while the patient is asleep. While the child was treated as a case of tetanus, she received inadequate sedation, which is an integral part of the routine management of these cases. In addition large amounts of parenteral medication and fluids were given without benefit of adequate prior sedation. Overstimulation may have accounted for the type and duration of the symptoms exhibited by this child.

It should be pointed out that it has been repeatedly shown that in the treatment of tetanus in childhood it is rarely necessary to use doses of antitoxin in excess of 100,000 units, and that this is best given in a single dose, either intravenously or by the combined intravenous and intramuscular routes. It has been similarly shown that with such a single dose protective levels of antitoxin persist in the blood stream for as long as six weeks. It is not only unnecessary, but may even be harmful to give repeated doses of antitoxin over a period of several days.

EXCRETION OF COMMON DRUGS IN BREAST MILK

Richard E. Houts, M.D.

The question of drug excretion through the milk of a nursing mother has always been a controversial subject. There have been many cases where a child was weaned simply because there was fear of transmission of some drug that was being administered to the mother concurrently. In more cases than not, the drug would not have been found in milk or would be transmitted in such minute quantities that it could not have possibly affected the child. Very few drugs are transmitted in quantities to produce therapeutic levels.

It has long been supposed that alcohol must not be taken by the lactating mother. There is evidence that alcohol is passed across the placenta but there is little evidence that a nursing infant can be affected by the amount transmitted through the milk. Although habitual imbibers seldom care to nurse their infants and infrequently have enough milk to do so, what milk is present is not harmful to the infant in so far as the alcoholic content is concerned.

Another drug that has been discussed widely concerning its transmission through breast milk is nicotine. One viewpoint has always maintained that the nursing mother should not smoke. Well controlled experiments on both rats and humans have proven that there is no measureable harm done to the infant of the mother who smokes. Wilson[1] has shown that when pregnant and lactating rats are given nicotine in drinking water in concentrations of 0.5, 1.0, 2.0 mgms. daily, no difference in birthweight, neonatal mortality or weight gain could be determined in a control group. Furthermore, Connally[2] observed four groups of mothers. One group, as a control, did not smoke. The other groups smoked "lightly," "moderately" and "heavily." The heavy smokers consumed about one or more packs per day. There was no statistical difference in the birth weight of the infant, weight gain, nausea and vomiting or mental reaction among the infants of the various groups. The milk supply of the mothers who smoked was not significantly lowered.

The question of transmission of laxatives through breast milk frequently arises because of their widespread use postpartem. One of the more complete experiments on this subject has been reported by Tyson, Shrader and Perlman[3]. These investigators observed the results upon the child of various laxatives and recorded both clinical and laboratory data. Aloin was found to pass through the milk but produced no effect upon the child. (Clinical effects were recorded as loose stool and actual diarrhea.) Phenolphthalein failed to be revealed by either clinical or laboratory tests.

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Cascara was observed to be readily transmitted through the milk and to affect the infant clinically. Calomel, Senna, and Rhubarb were not transmitted in detectable amounts. All these drugs were given in the usual therapeutic doses to the mother. It is possible if larger doses of some of these laxatives had been given, more evidence of transmission would have been noted. However, Cascara was the only laxative of those tested which will normally affect the infant clinically.

Tyson, Shrader and Perlman[4] also administered several of the barbiturates to nursing mothers in order to determine the extent of transmission through breast milk. Phenobarbital in sedative doses of 30.0 mgms. ($\frac{1}{2}$ gr.) every four hours produced the drug in the milk in 90% of the cases. Hypnotic doses of 90.0 mgms. ($1\frac{1}{2}$ grs.) in single dose revealed detectable amounts of the drug in 100% of the milk samples tested. Of the entire group of forty-one patients, only two infants showed any clinical effect from the drugs. Both of these infants received phenobarbital sodium through the milk when it was given the mother as a single dose of 90 mgms. ($1\frac{1}{2}$ grs.) a day. It can be concluded that the barbiturates are definitely transmitted and more commonly so when given in large single doses.

The opiates are of interest because of their use during the postpartem period. Kwit[5] gave a nursing mother 16 mgms. ($\frac{1}{4}$ grs.) of morphine sulfate and extracted her milk four hours later. Analysis revealed that in 170 cc. of milk there was less than 0.1 mg. of the drug present. Terwilliger and Hatcher[6] analyzed the milk of a confirmed morphine addict. The patient was given massive doses in order to subdue withholding symptoms. The milk was repeatedly analyzed and was found to contain either none or only a trace of the drug at each extraction. It would appear then that morphine is a relatively safe drug to use when indicated in sedation of a nursing mother. Kwit and Hatcher also investigated the transmission of codeine. Two patients received 192 mgms. in 32 mgm. doses every four hours and the milk was taken four hours after the last dose. Two other patients received 65 mgms. and the milk was taken four hours later. None of the various samples of milk taken from any of these women showed even a trace of codeine.

Dr. J. L. Way of the George Washington University has kindly provided the following unpublished data on the transmission of Demerol through breast milk. Milk was extracted from three women at two, four and six hour intervals after a single intramuscular dose of 100 mgms. Using a test which has a sensitivity of 0.5 mgms. per liter, Dr. Way failed to find any trace of the drug in the milk samples.

Tyson, Shrader and Perlman[7] also investigated the transmission of bromides through breast milk. Ten cases were given 6 grams (90 grs.) each day for three to five days. Thirty-eight samples of milk were drawn

at various times during the administration and of these, thirty-seven showed the presence of the drug in varying concentrations.   Clinical observation of the infants of these mothers revealed that all of them appeared to be less irritable and there were four cases of marked reactions to the drug.   It is apparent that bromides should not be used as sedatives for the nursing mother.

Kwit and Hatcher[8] administered sodium salicylate in divided doses of 640 mgms. (11 grs.) until a total of 4 grams (60 grs.) had been given. From 31 ounces of milk they recovered 1 mg. (1/60 gr.) of the drug.   After administering a total dose of 2 gms. (30 grs.) in divided doses of 320 mgms. (5 grs.) a total of 0.25 mgms. (1/250 grs.) of the drug was recovered from 26 ounces of milk.   Sodium salicylate seems quite harmless in so far as the nursing infant is concerned.

Since the advent of sulfonamides two questions have posed themselves, i.e. are the sulfonamides secreted in breast milk and would it be possible to administer the drug to a nursing child through the milk?   Hac et al.[9] gave twenty-five lactating women sulfonamides in 2 to 5 gram divided doses for three days.   It was found that for a very short period after a dose was given, the milk level was higher in some cases than the maternal blood level. It was also observed that the drug was secreted for as long as forty-eight hours after the last dose.   However, none of the twenty-five women secreted more than a total of 0.23 grams (about 4 grs.) in the five days.   The authors concluded that unless the infant possesses an idiosyncracy to the drug the sulfonamides will not effect him when transmitted through breast milk.   Steward et al.[10] recovered sulfonamides from the breast milk and also the blood and urine of the infant but it was concluded that the concentration was not great enough to produce any degree of toxicity nor was it practical to administer sulfonamides through the milk.

Penicillin has raised the same questions as the sulfonamides.   Burkhart and Hobby[11] reported on eleven normal lactating women who received penicillin intramuscularly.   The patients received from 50,000 units every three hours for twenty-four hours to 100,000 units every two hours for six doses.   Eight of the women secreted penicillin in the milk in amounts ranging from 0.007 to 0.06 units per cc.   The three women who secreted no penicillin had received 100,000 units in a single dose.   This experiment is of less importance clinically because of the lack of toxicity of the drug.

Kwit and Hatcher[12] also experimented with potassium iodide.   After giving doses which ranged from 325 mgms. to 650 mgms. three times a day, the milk was extracted and found to contain only traces of the drug.   There were no ill effects observed in the infants.

Terwillinger and Hattcher[13] analyzed milk from mothers who had been given 600 mgms. of Quinine.   Using a method which was capable of detect-

ing the drug in concentrations of 1,500,000 parts of milk, the authors could recover only 0.065 mgms. of Quinine in 85 cc.   The milk was extracted eight hours after administration of the drug.

There is experimental evidence to show that several metals used therapeutically are secreted in the milk.   These include arsenicals, lead and mercury.   However, any disease which is severe enough to necessitate the use of these drugs would sui generis be a contraindication to nursing.

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ERYTHROBLASTOSIS TREATED WITH
AN EXCHANGE TRANSFUSION

Case Report No. 103

Milton Greenberg, M.D.   T. 47–1008

Baby Boy T., age three days, was admitted to Children's Hospital on January 27, 1947 because of jaundice and a history of Rh incompatability. This infant was the product of a normal labor which was induced by medical means and rupture of the membranes at 37 weeks of cyesis because of an anti Rh titer in the mothers blood of 1–40. No previous titers were performed.

The infant was the result of the third pregnancy of this mother; two siblings are living and well. The mother was Rh negative and the father Rh positive. The birth weight of the infant was 4 pounds 7 ounces and immediately after birth he was placed in an incubator with continuous oxygen. No difficulty was encountered and baby appeared to have no respiratory embarrassment. No abnormalities were noted and no jaundice was present at birth. The liver and spleen were not enlarged.

A blood count taken immediately after birth showed 4,130,000 red blood cells with 15 gms. of hemoglobin. There were 2,000 nucleated red cells per cu. mm. Macrocytosis and polychromatophilia were noted. Prothrombin time was 35% of normal. The Rh factor was positive.

On the second day postpartem, jaundice was noted for the first time and transfusion of 45 cc. group O Rh negative blood was given to the infant. That same evening the blood count showed 5,060,000 red cells with 16 gms. of hemoglobin and very few nucleated red cells. However, the jaundice appeared deeper and the infant was transferred to Children's Hospital for a replacement transfusion.

Shortly after admission to the hospital, the infant was sent to the operating room where the exchange transfusion was performed. Blood was withdrawn from the radial artery at the wrist and at the same time 400 cc. citrated group O Rh negative blood in which half the plasma had been removed was introduced into the ankle vein.

After this procedure, the infant was returned to the incubator for the next six hours. He appeared more alert and active. However, suddenly and without apparent cause the infant expired six and one half hours after completion of the transfusion.

Comparison of the blood before and after replacement transfusion is as follows:

	Before	*After*
Icterus Index	200 Units	150 units
Total Protein	5.86%	4.48%
Rh factor	Positive	Negative

DISCUSSION

E. Clarence Rice, M.D.: Necropsy findings disclosed a premature, jaundiced infant weighing 2,200 grams. There was no hepatic enlargement; however, the spleen was moderately enlarged. A small amount of orange colored fluid was found in the peritoneal cavity. The brain had a yellow color and microscopically small hemorrhages were found in the cortex. The liver bore the brunt of the damage showing many collections of erythroblasts, areas of hematopoesis, degenerative changes in the polygonal cells with a slight increase of fibrous tissue. The epithelium of the renal tubules were stained dark by the icterus and revealed some degeneration. The findings were typical of those seen in erythroblastosis.

In 1901 Landsteiner placed blood transfusion on a satisfactory basis when he announced the discovery of the four human blood groups. In 1927 he and Levine reported the finding of additional blood factors, M, N and P. Reactions, however, followed transfusion of blood which could not be satisfactorily explained on an intra group incompatibility. Landsteiner and Weiner in 1941 reported on a new blood factor which they named Rh, because it was found that serum obtained from rabbits immunized with the blood of the Rhesus monkey would cause agglutination of the erythrocytes of 85% of all white persons. Later Weiner and Peters found that isoimmunization to the Rh factor could explain certain transfusion reactions. Years before Ottenberg and others had postulated that the changes noted in erythroblastosis of the newborn infant should be explained on some lack of compatibility between the blood of the fetus and the mother with resulting immunizing of the mother against the erythrocytes of her baby. Levine and other demonstrated that a large proportion of mothers delivered of erythroblastotic babies were Rh negative and suggested that such an incompatibility as evidenced between Rh positive baby and negative mothers was a logical explanation of the hematological and pathological changes seen in this condition.

Further work showed that there are at least eight Rh types. Subsequent work has demonstrated that not all erythroblastosis can be explained on the basis of the Rh factor and it is now known that another factor, termed Hr, of which there are now at least three types, and also the development of sensitivity of a group O mother's blood to the blood of fetal group A or B cells or possibly those AB can be causes of erythroblastosis also. The

problem becomes more complex with the demonstration of more than one kind of Rh isoantibodies in response to the Rh antigen.

It is now known that approximately 87% of all white persons, 95% of negroes and nearly 100% of members of the yellow, brown and black races are Rh positive.

The outstanding finding in erythroblastosis fetalis is the marked destruction of the red blood cells of the baby with a great increase in the number of nucleated red blood cells.   These may run as high as 250,000 per cu. mm. and are generally above 10,000.   Because of the large numbers of these cells the leucocyte counts of these babies are sometimes erroneously reported as being well over 100,000.   Correction for these cells will usually bring the white blood cell count down below 20,000.   The red blood cells are often macrocytic, many of the nucleated cells being macroblasts; the cells stain variably and show no lack of hemoglobin.   The number of red blood cells may decrease rapidly and the icterus may increase in inverse proportion. The Van den Bergh may be indirect or direct depending on the degree of liver damage and obstruction to the flow of bile.

Past experience tends to demonstrate the improved results obtained by using Rh negative blood in the transfusion of the erythroblastotic as compared with the use of random blood with no attention being paid to the donor's Rh factor.

In view of the evidence of liver pathology it would seem desirable on the part of the pediatrician to give adequate carbohydrate and protein along with choline, methionine and various other amino acids to repair the hepatic damage.

The question of the value of exsanguination or replacement transfusion cannot be definitely determined at the present time.   There appears to be some difference of opinion as to the general acceptance of replacement transfusion for all babies who have hemolytic disease of the newborn. I believe that Diamond and Weiner are not in agreement as to the procedure to be followed and I believe that it will take a year or more before enough data can be obtained to come to a satisfactory conclusion.

Benwood, Hunter, M.D., and John B. Ross, M.D.: In this case, one of Rh isoimmunization, the absence of anemia, jaundice or enlargement of the spleen and liver at birth is discouraging to the doctor who is trying to determine whether or not transfusion is necessary.   This lack of clinical findings, however, is not always associated with absence of laboratory findings.   It should be a routine procedure at the time of delivery to study thoroughly the cord blood of any baby born of an Rh negative mother whose blood shows Rh antibodies.   This should be done particularly when the antibody is elevated above a 1:8 dilution or has shown a sharp rise. The studies on the cord blood should be: (1) Complete blood count; (2)

Estimation of percentage of nucleated red cells; (3) Rh typing; (4) Titration of serum for antibody content; (5) Testing of cells for the presence of blocking antibodies (anti-human globulin test).

With these studies it is possible in most instances to estimate accurately the therapeutic procedure to be followed. In this instance an agglutinating antibody was present in a dilution of 1:64. This is a fairly high level and we know from subsequent events that the antibody must have been in the child's blood stream. Peculiarly enough, the antibody does not cause anemia but it did cause severe liver damage. This latter fact has been referred to recently by Darrow and Chapin[1]. These authors believe that there is a hypersensitivity factor involved which causes liver damage without causing erythrocyte destruction. This may very well explain many of the findings seen in this case as well as in many other similar cases of what appear to be deaths due to severe liver damage rather than as a result of marked erythrocyte destruction. If this is the case, then liver damage should be expected in such children and the elimination of the antibodies from the circulation should be of primary importance. In this case, however, a replacement transfusion was performed presumably after the liver destruction had occurred. If a replacement transfusion is to be used as a therapeutic measure it must be performed in the very first hours of life.

It has been our experience that these children appear in good condition for perhaps a few hours after delivery, but thereafter, for some unexplained reason, their condition undergoes radical change and they appear to be affected by some extensive process; frequently pallor and flaccidity are the main findings. Icterus may develop within 12 to 24 hours. Some of these changes may be the result of anoxemia and consequently it is well to have the child in an oxygen bed. A direct cord transfusion should be started as soon as possible after delivery and, if the laboratory findings indicate, the replacement transfusion carried out.

As regards the problem of whether to use Rh positive or Rh negative blood, there are two directions in which the answer has been sought. First, it has been found by many investigators, including Cassidy[2] at Children's Hospital, that Rh positive transfusions do not alleviate the anemia as quickly as Rh negative blood. With Rh negative blood the red cell count can be maintained for a longer period of time with fewer transfusions. The second approach, the theoretical, considers that the Rh positive red cells absorb antibody, and remove it from the circulation, thereby improving the child's condition, not by relieving any anemia but by eliminating antibody. It is our feeling that one should give Rh negative blood. If there is a consideration to eliminate antibody it should be done by replacement transfusion technique. If the attempt is made to eliminate antibody by Rh positive transfusion it is highly probable that the increased cell destruction will add to the already existing load on the liver.

In the preceding statements we have attempted to bring out the care of the new born child in which sensitization of the mother is evidenced by the presence of antibodies.   There is a certain amount of care, however, that should be instituted long before birth of the child and it has to do, of course, with the pre-natal care of both the mother and the fetus.   This care should be instituted at the time of the first visit the expectant mother makes to the obstetrician.   At this time, in addition to the usual tests for anemia and syphilis, Rh blood typing should be done.   If the mother is Rh negative her husband should be typed and if possible sub-grouped to determine whether he is homozygous or heterozygous for the Rh factor. If he is homozygous we know that all of his children will be Rh positive but if he is heterozygous half of his children will be Rh positive and half will be Rh negative.   If the father is Rh positive, the mother's antibody should be checked.   These tests are in most instances negative; however, the occasional case presents itself where the mother has been sensitized by previous transfusions or pregnancies.   With the knowledge of the presence or absence of antibodies in the early stages of pregnancy subsequent examinations will have real meaning.   Antibodies manifesting themselves late in pregnancy can be compared in strength to the examinations taken in the early period of pregnancy.   The first re-check should be done at the beginning of the seventh month of pregnancy and if still negative can be repeated at the beginning of the ninth month.   These are done to completely eliminate the possibility of sensitization complicating pregnancy. Examinations earlier have been found to be unnecessary since there is usually little change in the antibody before the fourth or fifth month. This is probably because the child's blood stream is rudimentary until that time.

If antibodies are present at the seventh month they should be re-checked every two weeks until the ninth month at which time they should be checked every week until delivery.   If there is any marked rise in the antibody content of the maternal blood it is evidence of increased sensitization. This being true it can be reasonably predicted that the infant will have some difficulty if this exposure has been long.   Consequently, labor should be induced whenever the size of the fetus and the condition of the cervix renders it feasible to deliver an otherwise healthy child.   Caesarian section has been recommended by some but, generally speaking, this has not been found to be necessary in most instances under our observation.

All preparations should be made before delivery of such children for immediate transfusion and study of the cord blood to determine whether or not replacement transfusion is necessary.   When the child is born and an exchange transfusion is contemplated, the cord should be cut one inch long and the child placed in a warm oxygen bed.   A cannula or catheter should be inserted into the umbilical vein and during the period of study

of the cord blood, 40–50, cc. of blood may be given. By the time that this
is completed, results of the laboratory studies are usually available and
further procedures can be determined at that time. The care of the new
born infants is of utmost importance.

Oxygen deficiency must be carefully watched for and any evidence of
anoxemia promptly relieved by increasing the oxygen flow. Warmth is
essential since these children are usually not robust and any prolonged
exposure associated with the transfusion should be guarded against. The
problem of prolonged trauma associated with any transfusion technique
must also be considered and steps taken to prevent fatigue.

Ralph Stiller, M.D.: A follow-up study of 29 living erythroblastotic
infants in the records of Children's Hospital revealed four of the 29 or 15%
to be neurologically unsound. There was no history of birth trauma in
these four and it was felt that this group represented clinical kernicterus.
All four were recognizably backward in the first year of life, two of them
showing signs in the neonatal period. It is of interest that only one of
these children, a $2\frac{1}{2}$ year old colored male, had classical signs of basal ganglia
disease. This bears out the reports in the literature in which reference is
frequently made to the widespread and non selective character of the
lesions found in kernicterus children.

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